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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,627	07/16/2003	Edgar Kaslin	4-31176B	3339

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,627	KASLIN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09693011.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claims 1-8, drawn to a transgenic animal, in the reply filed on 6/26/06 is acknowledged.

Claim Objections

Claims 1-6 are objected to because they encompass multiple inventions, i.e. transgenic or somatic recombinant animals (see the Restriction Requirement mailed 2/23/06). Upon election of an invention for examination in this application, the claims should be amended so that they read on only the elected invention.

Claim 5 is objected to because it fails to further limit claim 1 when it reads on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "whose genome" should be inserted before "comprising" in claim 1 to distinctly claim the instant invention.

Claim 8 recites the limitation "the soluble marker protein". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a transgenic *mouse* whose genome comprising a nucleic acid encoding a soluble marker protein inserted *between* a transcription start site and translation start site of an endogenous E-selectin gene, does not reasonably provide enablement for making any transgenic non-human *animal* comprising the genomic alteration at *any region* of an endogenous E-selectin gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The nature of the invention is directed to any transgenic non-human animal comprising in its genome a nucleic acid encoding a soluble marker protein, preferably SEAP, operably linked to an endogenous E-selectin promoter/regulatory sequence. The specification discloses the generation of a SEAP knock-in transgenic mouse having a SEAP cDNA inserted between transcriptional and translational start site of the endogenous E-selectin gene. The specification discloses that said transgenic knock-in

mouse is generated by homologous recombination of a target construct into mouse ES cells and subsequently introducing said ES cells into mouse blastocyst, which results in production of chimeric F1 heterozygous mouse, and mating of the F1 heterozygotes to produce homozygous mouse.

The breath of the claims is very broad. Claims 1-5 encompass any transgenic animal having in its genome a soluble marker protein functionally linked to an E-selectin promoter. However, the specification only discloses the generation of a SEAP knock-in transgenic mouse having a SEAP cDNA inserted between transcriptional and translational start site of the endogenous E-selectin gene by homologous recombination in embryonic stem cells. It is noted, ES cells have yet to be identified in animal species other than mouse. For example, *Kuroiwa et al* (Nature Genetics 2004;36:775-80) teach the ES cells suitable for gene targeting are not available for species other than mouse. *Moreadith et al* (J. Mol. Med., 1997, p. 214, *Summary*) note that "putative" ES cells found in other animals beyond mouse lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration for an art-recognized property of ES cells. The specification does not teach any other methods for generating a transgenic animal having a soluble marker linked to E-selectin in its genome, and thus fails to support the full scope of the claims. In view of such, the claimed invention does not appear to be enabled for the claimed genus of animals.

Concerning the position of genome insertion of a polynucleotide encoding a soluble marker protein, it is important because the position may influence the phenotype of the transgenic mouse. The phenotype of the transgenic mouse is a necessary

element that the specification must teach to enable one skilled in the art concerning how to use the transgenic mouse for its disclosed utility when considering the enablement of the invention. Without any phenotype, one skilled in the art would not know how to use the claimed transgenic mouse even though its genome comprises a soluble marker protein gene operably linked to E-selectin promoter. The specification teaches only how to use transgenic mice having the desired transgene-dependent phenotypic alteration. The mere capability to perform gene transfer in a given species is not enabling for the claimed transgenic animal because desired phenotype cannot be predictably achieved simply because the animal having the desired genotype. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al, 1992 Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al, 1993, Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant

expression (Wall, 1996 Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al.(1996) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al, 1996 J. Clin. Invest. 98, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997 Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997 Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron 1997, Molec. Biol. 7, page 256, lines 10-13). Further, even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund 2000, Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). Given the variation in transgene expression, and given the species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises any soluble marker operably linked to an endogenous E-Selectin

promoter, other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing the soluble marker, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

In the absence of specific guidance, one skilled in the art would not know how to use a transgenic mouse that does not exhibit the specific transgene-dependent phenotype disclosed in the instant specification, without undue experimentation. In view of the limited guidance in the specification and unpredictability in the art, one skilled in the art would have been required to engage in undue experimentation in order to make and use the full scope of the claimed transgenic or somatic recombinant animal.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications*

under 35 U.S.C. § 112, p 1 "Written Description" Requirement; Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 1-6 are directed to a transgenic animal having in its genome a polynucleotide encoding a soluble marker protein functionally linked to an E-selectin regulatory sequence. However, the specification only describes a single species of a transgenic knock-in mouse of the type claimed. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, claims 1-6 encompass the whole genus of "transgenic non-human animals" and include any and all transgenic non-human animals having in the genome a polynucleotide encoding a soluble marker protein functionally linked to an E-selectin regulatory sequence. Claims 1-8 further encompass an inserted transgene at any region of an endogenous E-selectin gene. However, the specification describes only a single species of knock-in mouse containing a SEAP in between the transcriptional and translational start site of the E-selectin and exhibits a specific phenotype, expression and secretion of the marker upon cytokine stimulation. Thus for the claims to meet the written description requirement, other representative species of transgenic non-human animals having in the genome a polynucleotide encoding a soluble marker protein functionally linked to an E-selectin regulatory sequence, and exhibit a specific phenotype as described in the specification, should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Next, it needs to be determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the claimed genus of transgenic non-human animals. Therefore, the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of "transgenic or somatic recombinant non-human animals." The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or using it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION *OF THE INVENTION.* THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED.*" (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of or representative species of knockin animals. Therefore, only the described mouse meets the written description provision of 35 U.S.C. §112, first paragraph.

The following art rejection applied even though the Examiner is aware of certain contradiction in the sections of enablement rejection and art rejection. In view of the Office policy for compact prosecution, all issues relevant will put forward in the first action on merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Contag et al* (US 6,217,847, IDS), in view of *Yang et al* (1997, Biotechniques 23: 1110-1114, IDS).

The claims are drawn to a transgenic mouse having in its genome a polynucleotide encoding a soluble marker protein functionally linked to a regulatory sequence of E-selectin.

Contag et al teach methods for detecting and localizing light originating from a mammal and animal models for disease states for localizing and tracking the progression of disease or a pathogen within the animal, and for screening putative therapeutic compounds effective to inhibit the disease or pathogen. *Contag et al* disclose a transgenic mouse having in its genome a polynucleotide encoding a soluble marker protein functionally linked to a promoter (e.g. figs 1c and 8). *Contag et al* go on to teach a promoter expressed in certain disease states can be used to mark affected areas in a transgenic animal and expression of the light-generating moiety can be used to monitor the effects of treatment. *Contag et al* particularly suggested a E-selectin promoter and luciferase marker protein (see col. 15, 1st paragraph to 5th paragraph). *Contag et al.* do not teach a transgenic mouse whose genome containing a E-selectin promoter operably linked to a SEAP.

Yang et al supplemented the deficiency of *Contag et al* by establishing it was well known in the art that alkaline phosphatase is a light-generating moiety and a useful tool for investigating the function of known or putative enhancer/promoter (see abstract). *Yang et al* teach a vector comprising the cDNA encoding SEAP (see page 1110, figure 1). *Yang et al* also teach that the chemiluminescence-based SEAP assay is about 10-fold more sensitive than similar assays using luciferase as the reporter enzyme (see abstract). *Yang et al* further teach that the SEAP having the advantage over luciferase because SEAP is secreted into cultured medium, thus makes it faster and easier to assay for its activity without disruption of the cells (see abstract).

It would have been obvious to one of ordinary skill of art to use SEAP as a marker protein instead of luciferase linked to E-selectin promoter in making a transgenic animal. The ordinary artisan would have been motivated to do so because of the teaching of *Yang et al.*, who teach that SEAP is more sensitive than luciferase, and the ease of use of SEAP in either chemiluminescent or fluorescent assay. The ordinary artisan would have reasonable expectation of success because the combined teaching of Contag et al., who teach a transgenic mouse containing a construct comprising E-selectin promoter operably linked to a luciferase reporter, and the teaching of *Yang et al* who teach a plasmid vector comprising SEAP cDNA (see page 1110, figure 1, pSEAP2) and the motivation to use SEAP as marker protein. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,632,978. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims encompass claim 1 of the cited patent. Claim 1 of the cited patent is directed to a species (SEAP) of the instantly claimed genus of animals whose genome comprising *a soluble marker protein* operably linked to an endogenous E-selectin promoter.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
July 17, 2006